

# Anticoagulation during Cardiopulmonary Bypass in Patients with Heparin-induced Thrombocytopenia Type II and Renal Impairment Using Heparin and the Platelet Glycoprotein IIb–IIIa Antagonist Tirofiban

Andreas Koster, M.D.,\* Marian Kukucka, M.D.,\* Friedhelm Bach, M.D.,† Oliver Meyer, M.D.,‡  
Thomas Fischer, M.D.,\* Fritz Mertzluff, M.D.,§ Matthias Loebe, M.D.,|| Roland Hetzer, M.D.,#  
Hermann Kuppe, M.D.\*\*

**Background:** Patients with heparin-induced thrombocytopenia type II require an alternative to standard heparin anticoagulation. However, in patients with renal impairment, anticoagulation during cardiopulmonary bypass with agents such as danaparoid sodium or r-hirudin are associated with hemorrhage. Anticoagulation with unfractionated heparins combined with prostacyclin, a potent platelet aggregation inhibitor, is associated with severe hypotension. The authors investigated a new concept using unfractionated heparins after platelet inhibition with the short-acting platelet glycoprotein IIb–IIIa antagonist tirofiban.

**Methods:** Ten patients with heparin-induced thrombocytopenia type II and renal impairment were enrolled in the investigation. All had heparin-induced thrombocytopenia type II antibodies present as proved by the heparin-induced platelet aggregation assay, the heparin–platelet factor 4 enzyme-linked immunosorbent assay, or both. In all patients, preoperative anticoagulation to an activated partial thromboplastin time of 40–60 s was performed with r-hirudin. Anticoagulation during cardiopulmonary bypass was achieved with a bolus of 400 IU/kg unfractionated heparins after a bolus of tirofiban 10  $\mu\text{g}/\text{kg}$  followed by an infusion of tirofiban at a rate of 0.15  $\mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$  until 1 h before conclusion of cardiopulmonary bypass. Additional unfractionated heparins were only administered if activated clotting time decreased below 480 s. Coagulation was monitored by a abciximab-modified TEG<sup>®</sup> and the adenosine diphosphate-stimulated (20  $\mu\text{M}$ ) platelet aggregometry. D-dimer concentrations, as a marker of venous thromboembolism, were measured before and 12, 24, and 48 h after surgery. Postoperative antithrombotic therapy was started immediately with r-hirudin to anticoagulation to an activated partial thromboplastin time of 40–60 s.

**Results:** The postoperative blood loss ranged from 110 to 520 ml. No patient needed reexploration. In no patient was there clinical evidence of thrombosis or embolism in the postoperative period or of a critical increase of the D-dimer concentrations, suggesting venous thromboembolism. Transfusion of platelets was necessary in only two patients.

**Conclusions:** The protocol is easy to perform and no increased postoperative bleeding and no thromboembolic complications occurred. The combination of unfractionated heparins and tirofiban may be an alternative to other anticoagulation strategies in patients with heparin-induced thrombocytopenia.

HEPARIN-INDUCED thrombocytopenia (HIT) type II is a potentially life-threatening complication. In contrast to HIT type I, the underlying mechanism of which has not been clearly identified and which is not associated with clinically relevant sequelae, immune-mediated HIT II is frequently associated with thromboembolic complications.<sup>1–4</sup> In patients with HIT II, antibodies against complexes of heparin and platelet proteins, in particular platelet factor 4, are generated. The antigen–antibody complexes bind to platelet receptors and induce platelet aggregation. This leads to a decrease of the platelet count and is often associated with thrombosis and embolism of the venous or the arterial system, or both, with a ratio of venous-to-arterial thrombotic events of 3–4:1.<sup>5,6</sup>

The diagnosis of HIT II is suspected clinically by the rapid decrease of the platelet count below 100,000/ $\mu\text{l}$  or to 50% of the baseline value after heparin administration. Confirmation of the diagnosis of HIT II can be achieved with laboratory tests. The presence of heparin–platelet factor 4 antibodies can be directly proved using an enzyme-linked immunosorbent assay or indirectly in functional tests, such as the C<sub>14</sub>-labeled serotonin release assay or the heparin-induced platelet-aggregation assay, both of which reveal platelet activation and aggregation in the presence of patient serum that contains HIT II antibodies, platelets, and heparin.<sup>7</sup>

The incidence of HIT II varies widely within the range of 1–20%,<sup>1–4</sup> which probably should be attributed to the use of different tests and criteria for the diagnosis. However, in only an estimated one third of patients with HIT II antibodies do thromboembolic events develop. In patients undergoing cardiac surgery, an incidence of approximately 1% has been reported,<sup>8</sup> and is associated with devastating complications, such as stroke, myocardial and mesenteric infarction, and pulmonary embolism.

In patients diagnosed with HIT II, an alternative anticoagulation must be used. In cardiac surgery, this poses a problem because anticoagulation of the cardiopulmonary bypass (CPB) system with unfractionated heparins (UFH) is the only well-established protocol. The heparinoid danaparoid sodium and the thrombin inhibitor recombinant hirudin (r-hirudin) have been successfully used in a large number of patients with HIT II during CPB.<sup>5,9–11</sup> However, when impaired renal function is present, no antidote is available. Severe hemorrhaging in patients with renal failure where these agents have been

\* Consultant, \*\* Chair, Department of Anesthesia, || Vice Chair, # Chair, Department of Thoracic and Cardiovascular Surgery, Deutsches Herzzentrum Berlin. † Consultant, § Director, Clinic for Anesthesia and Intensive Care Medicine, Bethel, Bielefeld, Germany. ‡ Consultant, Institute for Transfusion Medicine, Charité, Campus Virchow, Berlin, Germany.

Received from the Department of Anesthesia, Deutsches Herzzentrum Berlin, Berlin, Germany. Submitted for publication April 3, 2000. Accepted for publication September 25, 2000. Supported by the Deutsches Herzzentrum Berlin.

Address reprint requests to Dr. Koster: Deutsches Herzzentrum Berlin, Augustenburger Platz 1, D-13353 Berlin, Germany. Address electronic mail to: koster@dhzb.de. Individual article reprints may be purchased through the Journal Web site, www.anesthesiology.org.

used during CPB have been described,<sup>10,12</sup> because these drugs are normally excreted and no antidote is available.

Early reports about CPB in patients with HIT II described the successful use of prostacyclin combined with UFH.<sup>13</sup> However, the use of prostacyclin is associated with marked hypotension. In addition, no reliable on-line monitoring of the antiplatelet effect is available.

Antagonists of the platelet glycoprotein (GP) IIb-IIIa receptor provide potent inhibition of platelet aggregation and have been evaluated in large clinical trials during interventional cardiology procedures.<sup>14,15</sup> These agents have been proved *in vitro* to inhibit platelet activation in HIT patients.<sup>16-20</sup> We report on the use of UFH and the short-acting platelet GP IIb-IIIa antagonist tirofiban in 10 patients with HIT II and impaired renal function for anticoagulation during CPB.

## Patients and Methods

After approval by the local ethics committee (Charité, Campus Virchow, Berlin, Germany) and informed consent, 10 patients diagnosed with HIT II and impaired function of the kidneys, as determined by a creatinine clearance less than 50 ml/min and a serum creatinine concentration more than 1.5 mg/100 ml were enrolled in this prospective investigation.

### *Diagnosis of Heparin-induced Thrombocytopenia II*

In three patients, the diagnosis of HIT II was proved during the immediate preoperative period in our hospital as a result of a decrease of the platelet count during heparinization to less than 100,000/ $\mu$ l and a positive result in the heparin-induced platelet-aggregation assay (minimum three of four sequences positive). Six patients had been previously diagnosed with HIT II. All of them revealed a decrease of the platelet count of less than 100,000 or more than 50% from baseline during heparin administration, they had a positive reaction in the heparin-induced platelet-aggregation assay, and three of them additionally exhibited the clinical events of thromboembolism, such as stroke ( $n = 1$ ), pulmonary embolism ( $n = 1$ ), and peripheral embolism ( $n = 1$ ). Only in one patient, who was diagnosed in another hospital, because of the unavailability of the heparin-induced platelet-aggregation assay, was the diagnosis based on clinical signs and a positive result with the heparin-platelet factor 4 enzyme-linked immunosorbent assay. This patient revealed a decrease of the platelet count from 145,000/ $\mu$ l to 35,000/ $\mu$ l during heparinization, which was followed by deep vein thrombosis. Additionally, the diagnosis was indirectly confirmed by an increase of the platelet count to 170,000/ $\mu$ l after a change of the anticoagulation to r-hirudin (Refludan; Hoechst, Frankfurt, Germany). In all patients diagnosed in another

hospital, the actual presence of HIT II antibodies was proved in the heparin-platelet factor 4 enzyme-linked immunosorbent assay (Stago; Asniers-sur-Seine, France) before surgery.

The preoperative anticoagulation for all patients was performed by the intravenous application of r-hirudin. After a bolus of 5 mg, the continuous infusion was started with 2 mg/h. The infusion was adjusted until an activated partial thromboplastin time of 40–60 s was reached as the target value. In all patients, a rapid increase of the platelet count was observed after cessation of the heparin administration and initiation of anticoagulation with r-hirudin. The anticoagulation was maintained until the patient reached the operating room.

### *Anesthesia and Intraoperative Anticoagulation*

Anesthesia was performed according to the departmental standard with a totally intravenous technique that used midazolam, etomidate, sufentanyl, and pancuronium for induction and sufentanyl, propofol, and pancuronium for the maintenance of anesthesia. Monitoring included a radial arterial line; a trilumen central venous catheter, and a introducer with a non-heparin-coated pulmonary artery catheter for continuous cardiac output measurement (Baxter, Oakland, CA) *via* the right internal jugular vein. Cardiopulmonary bypass was performed according to the departmental standard with the use of non-heparin-coated lines, a roller pump, and moderate hypothermia (30–32°C). In one patient, thromboendarterectomy of the pulmonary artery was performed with deep hypothermia (18°C). In all patients, aprotinin (Antagosan; Hoechst, Frankfurt, Germany) was administered with a bolus of  $2 \times 10^6$  kallikrein inhibiting units to the patient,  $2 \times 10^6$  kallikrein inhibiting units for the priming solution, and a continuous infusion of 500,000 kallikrein inhibiting units/h during CPB. At the beginning of surgery, the r-hirudin infusion was stopped. Ten minutes before cannulation for CPB, a bolus of tirofiban (Aggrastat; MSD, Haar, Germany) of 10  $\mu$ g/kg was given and followed by a continuous infusion of  $0.15 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ .<sup>16</sup> Five minutes after the bolus of tirofiban, a bolus of 400 IU/kg UFH (Liquemin; Roche, Grenzach-Wylen, Germany) was administered. The CPB was started when a target activated clotting time (ACT) value of 480 s was achieved. During perfusion, additional boluses of UFH were given if the ACT decreased below a value of 480 s. The continuous infusion of tirofiban was stopped 1 h before the anticipated cessation of CPB. After perfusion, the CPB lines were emptied and infused into the patient. The necessary dosage of protamine was determined by the Hepcon HMS (Medtronic, Minneapolis, MN) and by total reversal of heparin after protamine application was confirmed *via* the low-range cartridge.

### Monitoring of Coagulation and Guidelines for Transfusions

Monitoring of platelet function was performed with the 20  $\mu\text{M}$  adenosine phosphate-stimulated platelet aggregometry (Mölab; Bio-Data Corporation, Philadelphia, PA) in citrated platelet-rich plasma. Platelet-rich plasma was prepared by centrifugation at 800 r/min for 15 min, and aggregation was measured at a stir rate of 900 r/min at a temperature of 37°C.

A four-channel kaolin TEG® (ROTEG; Dynabyte, Munich, Germany) was performed with two baseline channels and two additional channels that contained abciximab 5  $\mu\text{g}/\text{ml}$  (ReoPro; Lilly, Bad Homburg, Germany) for discrimination of the influence of the platelet glycoprotein IIb-IIIa receptor inhibition on the clot strength as observed by the maximum amplitude. The channels were prepared according to the following:

Baseline channel: 300  $\mu\text{l}$  citrated whole blood + 20  $\mu\text{l}$  kaolin solution (50 ml  $\text{CaCl}_2$  0.645% + 100  $\mu\text{l}$  kaolin) + 20  $\mu\text{l}$   $\text{CaCl}_2$  [0.2 M, buffered; Dynabite, Munich, Germany]).

Abciximab channel: 300  $\mu\text{l}$  citrated whole blood + 20  $\mu\text{l}$  kaolin solution + 20  $\mu\text{l}$   $\text{CaCl}_2$  + 35  $\mu\text{l}$  abciximab (ReoPro; Lilly, Bad Homburg, Germany).

According to previous investigations, a maximum amplitude of 40–50 mm using the kaolin activator was evaluated as normal.

The platelet aggregometry was performed before surgery, after the bolus of tirofiban, before heparin administration, and at intervals of 60 min after the application of tirofiban until the patient was transferred to the intensive care unit. The abciximab-modified TEG®, because it contained no heparinase, was only performed before surgery, after the tirofiban bolus, before heparin, and after protamine application at intervals of 60 min. The ACT was measured before closure of the chest.

Fresh frozen plasma was given according to the clinical demands and at the discretion of the attending anesthesiologist.

Platelet concentrates were only transfused under the condition of a prolonged ACT value of more than 150 s after protamine administration, persistent clinical evidence of microvascular bleeding, thrombocytopenia (fewer than 100,000/ $\mu\text{l}$ ), and a suppressed maximum amplitude (fewer than 30 mm) in the baseline TEG®.

### Postoperative Anticoagulation

Immediately after the arrival in the intensive care unit, a continuous infusion (5 mg/h) of r-hirudin was started and adjusted to a target activated partial thromboplastin time value of 40–60 s. Platelet counts were monitored every 4 h over a period of 12 h and twice daily thereafter until the patient was discharged.

In the case of a decrease of the platelet count, a HIT II reaction resulting from residual antigen-antibody complexes was suspected, and the r-hirudin dose increased to an activated partial thromboplastin time of 60–80 s. After discharge from the intensive care unit, the anticoagulation was changed according to the departmental standards to either aspirin or coumadins.

### Detection of Thromboembolism and Measurement of D-dimers

The patients were examined twice daily for signs of thromboembolism, which included investigation for the occurrence of embolic splits by inspection, auscultation and pulse status of the arteries, palpation of the abdomen to exclude mesenteric infarction, and neurological investigation to rule out stroke. In the case of suspected thromboembolism, further radiologic diagnosis was undertaken using computed tomography, arterial angiography, and Doppler sonography. D-dimers, as a noninvasive marker of venous thromboses, were measured at 12-h intervals during the first 48 h after surgery. The concentration of D-dimers was ascertained in citrated plasma by the use of the AUTO Dimertest (Organon Technika, Eppelheim, Germany). The reference range was 130–200  $\mu\text{g}/\text{l}$ . The creatinine kinase concentration

**Table 1. Biometric Data, Laboratory Data, and Surgery**

Patient	Sex	LVEF (%)	Age	Creatinine (mg/dl)	CC (ml/min)	Diagnoses and Coexisting Diseases	Surgery
1	Male	45	65	1.7	44	Mitral valve thromboses	Re-MVR
2	Male	35	32	2.1	38	Mitral valve thrombosis	Re-MVR
3	Female	60	28	1.8	43	Two-vessel disease, aortic stenosis, diabetes	AVR + 2 $\times$ CABG
4	Male	35	73	2.2	42	Endocarditis and aortic root abscess, COLD	ARR <sup>HG</sup>
5	Female	25	75	1.9	39	Three-vessel disease, COLD	Re-CABG 4 $\times$
6	Male	35	45	3.2	34	Three-vessel disease, diabetes	CABG 3 $\times$
7	Male	35	47	2.0	37	Aortic regurgitation mitral stenosis	AVR + MVR
8	Male	35	54	2.1	42	Mitral, tricuspid valve regurgitation	MVR, TVR
9	Female	41	43	2.4	39	Three-vessel disease, diabetes	CABG 3 $\times$
10	Female	70	25	3.1	29	Pulmonary artery embolism, diabetes	PATEA

LVEF = left ventricular ejection fraction; CC = creatinine clearance; MVR = mitral valve replacement; AVR = aortic valve replacement; CABG = coronary artery bypass graft; COLD = chronic obstructive lung disease; ARR<sup>HG</sup> = aortic root replacement with homologous graft and coronary reimplantation; TVR = tricuspid valve reconstruction; PATEA = thromboendarterectomy of pulmonary artery.

**Table 2. Duration of CPB, Transfusions, and Postoperative Chest Tube Drainage**

Patient	Duration of CPB (min)	ACT (s)	RBC	FFP	RDP	Chest Tube Drainage, 12/h (ml)
1	87	135	0	0	0	250
2	78	141	2	3	0	310
3	85	115	0	0	0	450
4	187	145	4	6	2	470
5	110	123	2	3	0	110
6	67	141	2	3	0	520
7	134	125	4	6	0	320
8	125	132	2	3	0	340
9	97	127	2	0	0	410
10	251	141	2	6	1	390

RBC = red blood cell concentrates; CPB = cardiopulmonary bypass; ACT = activated clotting time; FFP = fresh frozen plasma; RDP = random donor platelets

(critical value, > 100 U/l; creatinine kinase MB only measured in case of creatinine kinase concentration being > 100 U/ml) and troponin I concentrations (critical value, > 4.0 ng/ml), as markers for myocardial infarction, were measured routinely once daily.

#### Statistical Analysis

All values are presented as mean  $\pm$  SD. The statistical analysis was performed using repeated-measures analyses of variance with the use of the Scheffé F test. A *P* value less than 0.01 was determined to be significant.

## Results

#### Biometric Data

The biometric data, preoperative diagnoses, preoperative laboratory data, and the surgery performed are presented in table 1.

The CPB time ranged from 67 to 221 min (table 2). During perfusion, none of the patients needed an additional bolus of heparin because of a persistent prolongation of the ACT being more than 480 s. None of the patients required a continuous infusion of vasoconstrictors because of marked hypotension while undergoing perfusion. During surgery, eight patients had a platelet count decrease to a range of 46–72% when compared with the baseline values (table 3). Only in two patients

was a transfusion of platelet concentrates necessary. Transfusions of red blood cells and fresh frozen plasma were necessary in five patients. Two patients left the hospital without any transfusions (table 2).

The ACT measured after arrival at the intensive care unit ranged from 115 to 145 s. The postoperative chest tube drainage within the first 12 h ranged from 110 to 520 ml.

#### Platelet Function Test and Whole Blood Coagulation Tests

During CPB, the results of adenosine diphosphate-stimulated platelet aggregometry revealed a potent inhibition of platelet aggregation by tirofiban. The values obtained 2 and 3 h after termination of the tirofiban infusion for the adenosine diphosphate-stimulated aggregation remained depressed, whereas a significant increase of the maximum amplitude of the baseline TEG<sup>®</sup> when compared with the abciximab-modified TEG<sup>®</sup> channel, suggested a faster recovery from the effects of the antiplatelet agent (table 4).

#### Postoperative Outcome

Patients were admitted to the intensive care unit without catecholamine support (patients 1, 3, 6, 8, and 9) or with moderate catecholamine support (patients 2, 4, 5, 7, and 10; epinephrine, 0.1–0.2  $\mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ ). No

**Table 3. Results of the Platelet Count (1,000/ $\mu\text{L}$ )**

Patient No.	Preoperatively	Postoperatively				
		After Surgery	After 4 h	After 12 h	After 48 h	After 7 days
1	177	95	125	146	210	221
2	230	154	167	201	208	199
3	167	124	154	217	234	260
4	90	98*	123	234	267	310
5	210	97	129	254	246	230
6	325	234	237	279	310	367
7	243	124	176	203	240	267
8	165	97	133	167	170	174
9	220	120	168	179	198	234
10	120	130*	148	176	192	210

\* Intraoperative transfusion of platelets.



**Table 4. Results of the Platelet Function Test and Whole Blood Coagulation Tests**

Before Tirofiban			After Tirofiban			After 1 h CPB	1 h after CPB			2 h after CPB			Before Chest Closure
ADP (%)	B-TEG® (mm)	A-TEG® (mm)	ADP (%)	B-TEG® (mm)	A-TEG® (mm)	ADP (%)	ADP (%)	B-TEG® (mm)	A-TEG® (mm)	ADP (%)	B-TEG® (mm)	A-TEG® (mm)	ACT (s)
82 ± 4.9 (n = 10)	41 ± 4.3* (n = 10)	7.1 ± 2.1 (n = 10)	12.5 ± 2.7† (n = 10)	11 ± 2.3*‡ (n = 10)	4.1 ± 1 (n = 10)	10.1 ± 2.3† (n = 10)	17 ± 3.5† (n = 10)	24 ± 3.0*‡ (n = 10)	8 ± 0.5 (n = 10)	37 ± 10.7† (n = 10)	37 ± 5.1* (n = 10)	9.2 ± 1.8 (n = 10)	137 ± 5.5 (n = 10)

\* Significantly increased ( $P < 0.01$ ) compared with value of abciximab TEG®. † Significantly decreased ( $P < 0.01$ ) compared with adenosine diphosphate (ADP; 20  $\mu$ M)-stimulated platelet aggregation before tirofiban administration. ‡ Significantly decreased ( $P < 0.01$ ) compared with baseline value before tirofiban administration.

CPB = cardiopulmonary bypass; B-TEG® = baseline thromboelastogram; A-TEG® = abciximab thromboelastogram; ACT = activated clotting time.

patient needed reexploration. All patients were discharged from the intensive care unit within 24 h. No additional transfusions were necessary after surgery.

Frequent precise clinical investigation in none of the patients revealed any evidence for intra- or postoperative thromboembolic events. Therefore, no more invasive radiologic investigations were carried out. All patients left the hospital in accordance with a normal schedule of between the 7th and 10th postoperative day.

#### *Cardiopulmonary Bypass Clot Formation*

There were no intraoperative signs of clot formation in the CPB as witnessed by an increased in-line pressure of the oxygenator ( $> 400$  mmHg). After surgery, the CPB systems were examined for clot formation. There was no evidence of thromboses of the CPB systems after the visual examination of the systems.

#### *Concentrations of D-dimers, Platelet Counts, Creatinine Kinase, Creatinine Kinase MB, and Troponin I*

No patient revealed a preoperative increased concentration of D-dimers (range, 141–178  $\mu$ g/l; table 5). The D-dimer concentrations 12 h after surgery ranged from 156 to 298  $\mu$ g/l, whereas the values obtained after 24 h ranged from 144 to 230  $\mu$ g/l, and the values obtained after 48 h ranged from 132 to 212  $\mu$ g/l. No patient exhibited a decrease of the platelet count during the postoperative period (table 3). In no patient was there laboratory evidence of myocardial infarction as observed by a critical increase of the creatinine kinase concentrations ( $37 \pm 15$  U/l) or troponin I concentrations ( $0.7 \pm 0.15$  ng/ml).

## **Discussion**

Cardiac surgery that involves CPB was performed in series of 10 patients with both HIT II and preoperative impaired function of the kidneys. In all patients, anticoagulation during CPB was accomplished using UFH after inhibition of platelet aggregation with the short-acting platelet GP IIb-IIIa receptor antagonist tirofiban. The postoperative chest tube drainage was comparable with similar procedures that used only UFH as the anticoagulant. In none of the patients was there clinical evidence for intra- or postoperative arterial or venous thromboses and embolisms.

The current data suggest that in patients with HIT II and renal impairment, the combined use of UFH and the short-acting GP IIb-IIIa inhibitor tirofiban during CPB is a promising, easy to perform, new alternative option to established concepts that use danaparoid sodium or hirudin, both of which are associated with increased hemorrhaging in the case of renal impairment.<sup>10,12</sup> Moreover, the use of a GP IIb-IIIa inhibitor appears to be an improvement when compared with prostaglandins and the antiplatelet agent, which are also associated with severe hemodynamic side effects.

In contrast to abciximab (ReoPro), tirofiban binds competitively to the GP IIb-IIIa receptor and involves shorter inhibition of platelet function. The short half-life of approximately 2 h and the predominantly biliary elimination ( $> 70\%$ ) favor this agent for the purpose of short, controlled inhibition of platelet aggregation, particularly in patients with renal impairment.<sup>21</sup>

D-dimers have a high negative predictive value for the incidence of venous thrombosis and pulmonary embolism.<sup>22</sup> The fact that a high postoperative pathologic D-dimer concentration was observed in none of the

**Table 5. Results of the D-dimer ( $\mu$ g/l) Determination**

	Before CPB	12 h Postoperatively	24 h Postoperatively	48 h Postoperatively
Mean $\pm$ SD	167 $\pm$ 20.8	205 $\pm$ 16.7	198 $\pm$ 18.1	169 $\pm$ 17.3
Range	141–178	156–298	144–230	132–212

\* Values are significantly ( $P < 0.01$ ) increased compared with preoperative value.

CPB = cardiopulmonary bypass.

patients and that the D-dimer concentrations decreased rapidly after surgery provides strong evidence that no venous thromboses or pulmonary embolism occurred within the investigation period. The moderate increase in the D-dimer concentrations after surgery can be attributed to operative trauma and extracorporeal circulation.<sup>22</sup> Moreover, there was no clinical evidence of arterial thrombosis or embolism or laboratory evidence of myocardial infarction. No patient exhibited a decrease of the platelet count in the postoperative period. Thus, this investigation for the first time provides evidence that platelet GP IIb-IIIa antagonist tirofiban effectively inhibited HIT II-associated thromboembolism *in vivo*, particularly in view of the confirmed actual antibody status in all patients before surgery.

However, there is no information with regard to the persistence of heparin-platelet factor 4 antibody complexes, either in the plasma or after binding to the platelet FcγRII receptor. In consequence, with ongoing recovery of platelet aggregation, the patient is potentially at a residual risk of HIT II-associated complications developing that are the result of circulating or platelet-bound antigen-antibody complexes. Therefore, the immediate institution of an effective antithrombotic therapy is an integral part of the concept. As thrombin generation plays a pivotal role in HIT II-associated thromboembolism,<sup>23</sup> r-hirudin, the most potent thrombin inhibitor known, was used for thrombosis prophylaxis.<sup>24</sup> Despite the impaired function of the kidneys, the systemic application of lower doses (activated partial thromboplastin time, 40–60 s) of r-hirudin was not associated with postoperative hemorrhage.

Visible clot formation in the operation field at the conclusion of surgery and the results of the global coagulation test ACT reveal a fast restoration of coagulation. This observation is supported by the faster recovery of the maximum amplitude in the baseline channel of TEG®, whereas the abciximab channel of TEG® remained suppressed after termination of the tirofiban infusion. However, the adenosine diphosphate-stimulated platelet aggregation, in keeping with literature data, was still suppressed.<sup>15</sup> This divergence between the results of the whole blood coagulation tests and the persistent inhibition of platelet aggregation in the adenosine diphosphate-stimulated platelet aggregation in citrated platelet-rich plasma needs further elaboration.

One limiting factor of this investigation is that only venous thromboses and pulmonary embolism could be ruled out as thromboembolic events by the use of the D-dimer test. Arterial embolism and thrombosis, except myocardial infarction, which was ruled out by the laboratory markers creatinine kinase and troponin I, were not excluded by repetitive and more invasive radiologic methods. However, the frequent careful clinical investigation of the patients, the uneventful postoperative course, and the increasing postoperative platelet counts

provided no evidence for the occurrence of such complications, which might have justified more invasive diagnostic procedures, particularly in view of the reported ratio of 3 or 4:1 for venous to arterial embolism.<sup>5,6</sup>

However, although the efficiency of the tirofiban protocol has been validated in large clinical trials, CPB might have an influence on the effect of the agent. Therefore, close control of the tirofiban effect *via* a specific point-of-care monitoring system is highly desirable.

We conclude that the combined use of UFH with tirofiban for anticoagulation during CPB and immediate postoperative antithrombotic therapy of r-hirudin was not associated with clinical or biochemical evidence of thromboembolism in 10 patients with HIT II and a presence of HIT II antibodies. No patient exhibited postoperative hemorrhage complications. The protocol appears to be a promising option for patients with HIT II and renal impairment. Because of the ease of use, it may be an attractive alternative to other anticoagulation concepts for patients with HIT II during CPB. Further validation in clinical trials is necessary.

The authors thank Ms. Tonie Derwent, Deutsches Herzzentrum Berlin, Berlin, Germany, for her editorial assistance.

## References

1. Slaughter TF, Greenberg CS: Heparin-associated thrombocytopenia and thrombosis: Implications for perioperative management. *ANESTHESIOLOGY* 1997; 87:667–75
2. Shorten GD, Commuale ME: Heparin-induced thrombocytopenia. *J Cardiothorac Vasc Anesth* 1996; 10:521–30
3. Brieger DB, Mak KH, Kottke-Merchant K, Topol EJ: Heparin-induced thrombocytopenia. *JACC* 1998; 31:1449–59
4. Kibbe MR, Rhee RY: Heparin-induced thrombocytopenia: Pathophysiology. *Semin Vasc Surg* 1996; 9:284–91
5. Magnani HN: Management of patients with heparin-induced thrombocytopenia (HIT): An overview of 230 patients treated with Orgaran (Org 10172). *Thromb Haemost* 1993; 70:554–61
6. Warkentin TE, Kelton JG: A 14 year study of heparin-induced thrombocytopenia. *Am J Med* 1996; 101:502–7
7. Greinacher A, Michels I, Kiefel V, Mueller Eckard C: A rapid and sensitive test for diagnosing heparin-induced thrombocytopenia. *Thromb Haemost* 1991; 66:734–6
8. Walls JT, Curtis JJ, Silver D, Boley TM: Heparin-induced thrombocytopenia in patients who undergo open heart surgery. *Surgery* 1990; 108:686–93
9. Koster A, Kuppe H, Hetzer R, Sodian R, Crystal GJ, Mertzluft F: Emergency cardiopulmonary bypass in five patients with heparin-induced thrombocytopenia type II employing recombinant hirudin. *ANESTHESIOLOGY* 1998; 89:777–80
10. Koster A, Pasic M, Bauer M, Kuppe H, Hetzer R: Recombinant hirudin as anticoagulant for cardiopulmonary bypass in patients with heparin-induced thrombocytopenia type: II. Importance of preoperative renal function. *Ann Thorac Surg* 1999; 69:137–41
11. Magnani HN, Beijering R, ten Cate JW, Chong BH: Orgaran anticoagulation for cardiopulmonary bypass in patients with heparin-induced thrombocytopenia. *New Anticoagulants for the Cardiovascular Patient*. Edited by Pifarre R. Philadelphia, Hanley and Belfus, 1997, pp 487–500
12. Westphal K, Martens S, Strouhal U, Matheis G, Lindhoft Lst E, Wimmer-Greinecker G, Lischke V: Heparin-induced thrombocytopenia type II: Perioperative management using danaparoid sodium in a coronary artery bypass patient with renal failure. *Thorac Cardiovasc Surg* 1997; 45:318–20
13. Kraenzler EJ, Starr NJ: Heparin-induced thrombocytopenia: Management of patients for open heart surgery. Case reports describing the use of iloprost. *ANESTHESIOLOGY* 1988; 69:964–7
14. Ferguson JJ, Waly HM, Wilson JM: Fundamentals of coagulation and glycoprotein IIb/IIIa receptor inhibition. *Eur Heart J* 1998; 19(suppl D):3–9
15. McClellan KJ, Goa KL: Tirofiban: A review of its use in acute coronary syndromes. *Drugs* 1998; 56:1067–80
16. Mak KH, Kottke-Marchant K, Brooks LM, Topol EJ: In vitro efficiency of platelet glycoprotein IIb/IIIa antagonist in blocking platelet function in plasma of

patients with heparin-induced thrombocytopenia. *Thromb Haemost* 1998; 80: 989-93

17. Haas S, Walenga JM, Jeske WP, Fareed J: Heparin-induced thrombocytopenia: The role of platelet activation and therapeutic implications. *Semin Thromb Haemost* 1999; 25(suppl 1):67-75

18. Jeske WP, Walenga JM, Szatkowski E, Ero M, Herbert JM, Haas S, Bakhos M: Effect of glycoprotein IIb/IIIa antagonists on the HIT serum induced activation of platelets. *Thromb Res* 1997; 88:271-81

19. Herbert JM, Savi P, Jeske WP, Walenga JM: Effect of SR121566A, a potent GP IIb-IIIa antagonist, on the HIT serum/heparin-induced platelet mediated activation of human endothelial cells. *Thromb Hemost* 1998; 80:326-31

20. Polgar J, Eichler P, Greinacher A, Clemetson KJ: Adenosine diphosphate (ADP) and ADP receptor play a major role in platelet activation/aggregation induced by sera from heparin-induced thrombocytopenia patients. *Blood* 1998; 91:549-54

21. Vickers S, Theoharides AD, Arison B, Balani SK, Cui D, Duncan CA, Ellis JD,

Gorham LM, Polsky SL, Prueksaritanont T, Ramjit HG, Slaughter DE, Vyas, KP: In vitro and in vivo studies on the metabolism of tirofiban. *Drug Metab Dispos* 1999; 27:1360-6

22. Bounameaux H, deMoerloose P, Perrier A, Reber G: Plasma measurement of D-dimer as diagnostic aid in suspected venous thromboembolism: An overview. *Throm Haemost* 1994; 71:1-6

23. Warkentin TE, Hayward CPM, Boshkov LK, Santos AV, Sheppard JA, Bode AP, Kelton JG: Sera from patients with heparin-induced thrombocytopenia generate platelet derived microparticles with procoagulant activity: An explanation of the thrombotic complications of heparin-induced thrombocytopenia. *Blood* 1994; 84:3691-9

24. Greinacher A, Volpel H, Janssens U, Hach-Wunderle V, Kamkes-Matthes B, Eichler P, Mueller-Velten HG, Potzsch B: Recombinant hirudin (lepirudin) provides safe and effective anticoagulation in patients with heparin-induced thrombocytopenia: A prospective study. *Circulation* 1999; 99:73-80